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REQUEST FOR GRANT OF A PATENT

8418303

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* P:3059

II Title of Invention "NOVEL COMPOUNDS"

A

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) THE WELLCOME FOUNDATION LIMITED,

Country United Kingdom State ADP Code No.

Address 183-193 Euston Road,
London, NW1 2BP.

Name (of second applicant, if more than one) THE GENERAL HOSPITAL Corporation

Country U. S. A. State

Address 55 Fruit Street,
Boston, Massachusetts, United States of America

Form 47/77
2.7.85

IV Inventor (see note 3)

[redacted]

(b) A statement on Patents Form No 7/77 is/will be furnished

V Name of Agent (if any) *(See note 4)* J. A. KEMP & CO. | ADP CODE NO

VI Address for Service (See note 5) 14, South Square
Gray's Inn
LONDON WC1R 5EU

VII Declaration of Priority (See note 6)

Country	Filing date	File number
NONE		

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VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)

Earlier application or patent number ..... and filing date .....

V4919*

IX Check List *(To be filled in by applicant or agent)*

A	The application contains the following number of sheet(s)		B	The application as filed is accompanied by:-	
1	Request	Yes Sheet(s)	1	Priority document	No
2	Description	14 Sheet(s)	2	Translation of priority document	No
3	Claim(s)	2 Sheet(s)	3	Request for Search	No
4	Drawing(s)	– Sheet(s)	4	Statement of Inventorship and Right to Grant	No
5	Abstract	– Sheet(s)			

X It is suggested that Figure No ..... of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)* J A Kemp & Co.

J. A. KEMP & CO. Authorised Agents

NOTES:

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5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.
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SHORT DURATION NEUROMUSCULAR BLOCKING AGENTS

The present invention relates to novel compounds, methods for the preparation of such compounds, pharmaceutical compositions containing them and their use in medicine as neuromuscular blocking agents of short duration high potency and quick onset. These compounds also have an unexpectedly high therapeutic ratio which makes the compound exceptionally safe.

In anesthesia, neuromuscular blocking agents are used to provide skeletal muscle relaxation during surgery and during intubation of the trachea. Neuromuscular blocking agents are used in practically every field of surgery. Because of the various demands of clinicians for neuromuscular blocking agents it has been recognized for over 25 years that there is a need for a short duration non-depolarizing agent.

In general there are two types of neuromuscular blocking agents in use, non-depolarizing and depolarizing.

The non-depolarizing agents include the long duration agents d-tubocurarine, pancuronium, gallamine, diallyltoxiferine, toxiferine, and the intermediate duration agents atracurium and vecuronium.

The depolarizing agents include succinylcholine and decamethonium. All the conventional non-depolarizing agents when used for producing skeletal muscle relaxation in surgery have a long duration of action, e.g. 60 to 180 minutes in humans.

The conventional depolarizing agents, on the other hand, provide muscle relaxation with duration of action shorter than that of the non-depolarizing agents. For example, succinylcholine provides a short duration of action of about 5 to 15 minutes of muscle relaxation in humans.

The long-duration non-depolarizing agent have inherent side effects. For example, gallamine and pancuronium may cause tachycardia, and d-tubocurarine and diallyltoxiferine may cause hypotension. The intermediate

duration and long duration agents lack a rapid onset of neuromuscular paralysis.

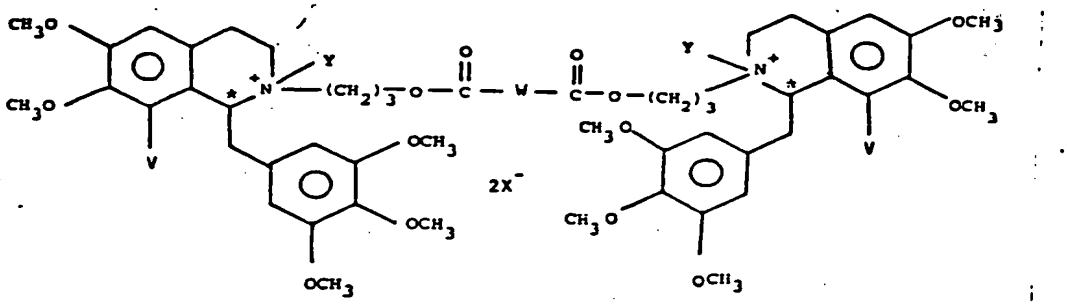
While these drugs can be pharmacologically antagonized with anticholinesterase agents, this necessitates the administration of a second drug which itself may have its own side effect, e.g., bradycardia, gut spasm and bronchorrhea. Thus, to overcome the aforementioned side effects of the anticholinesterase agents, a third drug, an anticholinergic agent, e.g., atropine, must also be given.

The only short-duration agent currently available for therapeutic use is the depolarizing agent, succinylcholine. The depolarizing agents to the best of the applicants' knowledge have no pharmacological antagonists. While in most cases there is no need to reverse the effects of the depolarizing agents, in certain patients the effects of succinylcholine are much prolonged because of abnormal metabolism of the agent by the patient.

The depolarizing agents due to their mode of action initially cause skeletal muscle contraction and stimulation of smooth muscles. They also cause the following side effects in certain instances: increased intraocular pressure and intragastric tension, cardiac arrhythmias, potassium release and muscle pain.

These side effects caused by the depolarizing agents are not caused by the non-depolarizing agents. It is, therefore, clearly evident that a neuromuscular blocking agent which would combine the short duration of the depolarizing agents with the relatively few side effects and the pharmacologic reversibility of the non-depolarizing agents would be beneficial.

European Patent Application No. 81110513.9 discloses that compounds of the formula (II):



(II)

wherein W is $-(CH_2)_2-$, V is methoxy, Y is C_{1-4} alkyl and X is an anion are useful in medicine as neuromuscular blocking agents of long duration.

European Patent Application No. 82110782.8 discloses that compounds of the formula (II) wherein V is methoxy, Y is C_{1-4} alkyl, X is an anion and W is $-(CH_2)_n-$ wherein n is 3-7 are useful in medicine as intermediate duration neuromuscular blocking agents.

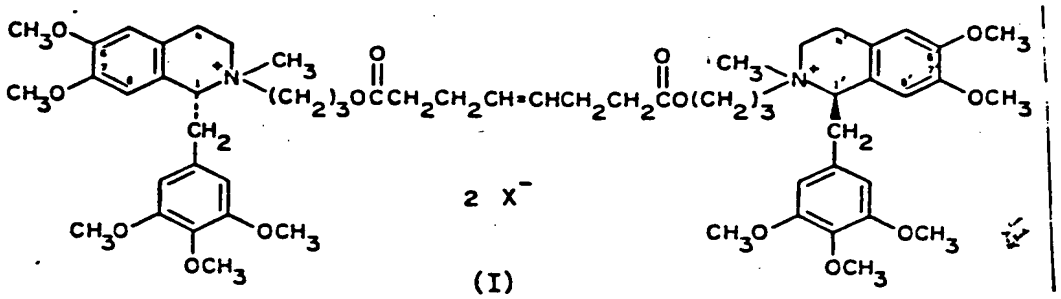
It has now been discovered that a novel group of compounds of the formula (II) wherein V is hydrogen, Y is methyl, X is an anion and W is a group $-CH_2CH_2-CH=CH-CH_2-CH_2-$ are potent neuromuscular blocking agents of short duration. These compounds have a non-depolarising mechanism of action, are pharmacologically reversible and have a rapid onset of action, a feature which is of great importance in emergency surgical procedures.

Those novel compounds in which the substituents about the carbon atom marked with an asterisk are in the R configuration (as defined below) have particularly beneficial properties and are believed to be free from any adverse side effects at the dosages that it is anticipated will be used clinically.

Surprisingly, it has been found that the enantiomeric compounds, i.e., those wherein the stereochemical configuration of the substituents about the

asterisked 1- and 1'-carbon atoms is S, can induce adverse cardiovascular effects, such as those associated with histamine release, at clinically useful neuromuscular blocking doses.

Accordingly, the present invention provides a compound of the formula (I):



(I)

wherein X^- is a pharmaceutically acceptable anion.

Formula (I) depicts the R configuration at the chiral carbons (carbon 1 and 1') of both isoquinolinium moieties. While it is believed that this represents the true absolute configuration at the chiral atoms of the compounds of formula (I), for the purposes of the instant application the configuration at carbons 1 and 1' of the compounds of formula (I) are designated as R and this is defined as the configuration obtained using (-)-5'-methoxylaudanosine, also identified as (-)-(R)-5'-methoxylaudanosine, the preparation of which is described in Example 1, in the preparation of the compounds of formula (I) according to the procedure of Example 1.

The compounds of the formula (I) exist in either the E or Z configurations with respect to the alkenic double bond. In addition, the substituents about each of the quaternary nitrogen atoms exist in either the R or the S configuration. As a result, for each of the geometric isomers (E or Z) there are three optical isomers, the RR-RR, RS-RS and RR-RS, (RR-RS is equivalent to

RS-RR isomer) making a total of six isomeric forms with the formula (I). The present invention provides the individual isomers of the formula (I) or mixtures of such isomers.

The three isomers of the E configuration, are preferred and are referred to hereinafter as Compound A.

The most preferred E isomer in terms of potency is that of the RS-RS configuration (Compound B). In a preferred aspect, the compounds of formula I are substantially free of any compound with S configuration at 1 and 1^1 posit

Since the activity of the compounds of the invention resides in the di-cation, the nature of the anion X^- is relatively unimportant. Suitable pharmaceutically acceptable anions include iodide, mesylate, tosylate, bromide, chloride, hydrogen sulphate, sulphate/2, phosphate/3, hydrogen phosphate/2, acetate, benzenesulphonate, hemisuccinate, succinate/2 maleate, naphthalenesulphonate and propionate.

The compounds of formula (I) as a mixture and the individual isomers per se disclosed are useful as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration, e.g., intramuscular or intravenous administration in solutio The compounds of the present invention shown in formula (I) are administere to subjects such as monkeys and humans and other mammals to achieve neuromuscular blockade. The dosage for each type of subject will vary because of the peculiarities of the species. However, a suitable intraveno amount or dosage of the compounds of formula (I) together in a mixture or as individual isomers to obtain paralysis in mammals would be 0.01 to 0.50 mg/kg of body weight, and most preferably, 0.025 to 0.3 mg/kg of body weight, the above being based on the weight of the di-cation which is the active ingredi The dosage for intramuscular administration is two to four times the intrave dose. The compounds of this invention are reversible using conventional

anticholinesterase agents such as neostigmine and edrophonium and appear to avoid the side effects associated with the conventional non-depolarizing agents.

The compounds of formula (I) are therefore useful for producing a short duration neuromuscular blockade in humans as well as in other mammals, and the present invention provides a method of producing such blockade in mammals by intravenously injecting a dose of 0.01 to 0.50 mg/kg to the mammal. It should be understood that the profile of neuromuscular blockade in a mammal such as a monkey is similar to humans and the compounds of formula (I) are considered short duration agents for the monkey.

The compounds may be presented in a pharmaceutical formulation for parenteral administration. The formulation may be an aqueous or non-aqueous solution or emulsion in a pharmaceutically acceptable liquid or mixture of liquids, which may contain bacteriostatic agents, antioxidants, buffers, thickening agents, suspending agents or other pharmaceutically acceptable additives. Alternatively the compounds may be presented as lyophilized solids for reconstitution with water (for injection) or dextrose or saline solutions. Such formulations are normally presented in unit dosage forms such as ampouls or disposable injection devices, or in multidose forms such as a bottle from which the appropriate dose may be withdrawn; all such formulations should be sterile.

The suitable unit dose to obtain a neuromuscular block for adult humans (~150 lbs or 70 kg) is 0.5 to 20 mg and most preferably 3.5 to 15.0 mg.

The compounds of this invention if desired may be administered in conjunction with depolarizing agents such as listed above.

Thus a suitable pharmaceutical parenteral preparation for administration to humans will preferably contain 0.1 to 5 mg/ml of the compounds of formula (I) of this invention in solution or multiples thereof for multi-dose vials.

A simple and preferred formulation is a solution of the compound of formula (I) in water or dextrose solution which may be prepared by simply dissolving the compound in pyrogen-free water or water containing dextrose, with or without a preservative and sterilizing the solution, or by dissolving the sterile compound in pyrogen-free, sterile water or a sterile dextrose solution under aseptic conditions.

The compounds of formula (I) may also be administered as an infusion of a dextrose solution or a saline solution, e.g., Ringer's solution.

The compounds may also be administered in other solvents (usually as a mixed solvent with water) such as alcohol, polyethylene glycol and dimethylsulphoxide. They may also be administered intramuscularly as a suspension or solution.

The compounds of formula (I) may be prepared by the coupling of an N-3-hydroxypropyl-1-(R)-5'-methoxylaudanosinium salt, preferably the chloride, with (E)- or (Z)-4-octene-1,8-dioic acid or a reactive derivative thereof such as the diacid chloride.

Example 1: (E)-(1R,1'R)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride

a. Compound A

To (±)-5'-methoxylaudanosine (46.4 g) in methanol (240 mL) was added (-)-dibenzoyltartaric acid monohydrate (45.2 g). The mixture was heated to

boiling, cooled at 5°C for 16 hrs and the (-)-(S)-5'-methoxylaudanosinium dibenzoyltartrate salt (35.6 g, 80%) was filtered and discarded. The mother liquors were made basic with concentrated aqueous NaOH and evaporated under vacuum. The solid residue was partitioned between H_2O (200 mL) and diethyl ether (2 x 150 mL). The ether phase was dried and evaporated to an oil (24.9 g). To the oil in methanol (128 mL) was added (+)-dibenzoyltartaric acid monohydrate (26.6 g). The mixture was heated to boiling and cooled at 5°C for 16 hrs. Crystals were collected and recrystallized from methanol until a constant specific rotation of $[\alpha]_D^{20} = +17.7°$ (1% EtOH) had been achieved. The yield of (+)-(R)-5'-methoxylaudanosinium dibenzoyltartrate as white crystals was 29.4 g (66%). A portion of the salt (15.0 g) in methanol (200 mL) was made basic with concentrated aqueous NaOH. The mixture was evaporated under vacuum and the residue was partitioned betwen H_2O (200 mL) and diethyl ether (2 x 200 mL). The combined ether layers were dried and evaporated under vacuum to yield 7.2 g (92%) of (-)-(R)-5'-methoxylaudanosine as a light yellow oil.

(-)-(R)-5'-Methoxylaudanosine (7.2 g), 3-chloropropanol (3.5 g), sodium iodide (5.6 g) and sodium carbonate (0.5 g) were refluxed in 2-butanone (125 mL) for 16 hrs. The white suspension was filtered hot and solvent removed from the filtrate under vacuum. The residual gum was triturated with hot ethyl acetate to remove excess 3-iodopropanol, dissolved in 200 mL methanol and passed through a column packed with Dowex® 1-X8 ion exchange resin (60 g). The eluant was stripped of solvent under vacuum to give the quaternary chloride salt (8.4 g) as an amorphous solid. The material was assayed by HPLC as a 2.3/1 mixture of the trans/cis diastereomers.

N-3-Hydroxypropyl-1-(R)-5'-methoxylaudanosinium chloride (2.3/1, trans/cis by HPLC, 2.5 g) was dissolved in 60 mL 1,2-dichloroethane at about

70°C. (E)-4-Octene-1,8-dioic acid chloride (0.5 g) (K. Sisido, K. Sei, and H. Nozaki, J. Org. Chem., 1962, 27, 2681) was added and the mixture was stirred at ambient temperature for 19 hrs. Solvent was removed under vacuum to give an amorphous solid which was dissolved in chloroform (25 mL) and washed with 5% aqueous sodium chloride solution (3 x 25 mL) to remove unreacted quaternary salts. The chloroform layer was dried and evaporated under vacuum to give an amorphous solid. Several impurities were substantially removed by washing with hot 2-butanone. Residual solvent was evaporated under vacuum and the resulting amorphous solid was dissolved in methanol, filtered and lyophilized to give 1.9 g of (E)-(1R,1'R)-2,2'-[4-octenedioylbis(oxytrimethylene)]bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride, Compound A, which was asaved by HPLC* as 44.6% RS-RS (trans-trans) diester (retention time 31.1 minutes), 42.4% RR-RS (cis-trans) diester (retention time 29.1 minutes), 7.5% RR-RR (cis-cis) diester (retention time 27.7 minutes) and 5.5% related substances (retention times less than 20 minutes).

^{1}NMR ($CDCl_3$): only those peaks assigned with certainty are reported: from TMS: 6.64 (s,H-5 for RR and RS, 2H), singlets at 6.42 and 6.26 (H-2', 6' for RS and RR respectively, 4H), singlets at 5.77 and 5.72 (H-8 for RR and RS respectively, 2H).

Calculated for $C_{58}H_{80}N_2O_{14}\cdot 2Cl\cdot 4H_2O$: C, 59.44; H, 7.57; N, 2.39; Cl, 6.05. Found: C, 59.36, H, 7.60; N, 2.36; Cl, 5.99.

Specific rotation: $[\alpha]_D^{20} = -58.6°$ (2% in H_2O, calculated on the basis of the anhydrous dichloride).

*Column: Whatman Partisil 5, 25 cm x 4.6 mm ID - Mobile Phase: acetonitrile: water (84:16) with 1% phosphoric acid (85%) overall, Flow rate: 0.4 ml/minute Detection: 280 nm, 0.05 AUSS - Sample Prep: 0.25 mg/ml in 90% acetonitrile

b. Compound B

A mixture (1.0 g) of essentially the RR-RR, RR-RS diesters (as prepared above) was dissolved in ethanol (5 mL) and deposited onto a Waters prep LC/System 500A (Waters Associates, Milford, Ma. 01757) silica gel cartridge. The material was eluted with ethanol/methanol, 1/1, containing tetramethylammonium chloride (1.0 g/L). Appropriate fractions were combined and solvent was removed in vacuo. The residual white solid was triturated with chloroform and tetramethylammonium chloride was removed by filtration. The chloroform solution was extracted with water. The aqueous phase was made 5% in sodium chloride and extracted with chloroform. The chloroform solution was dried over magnesium sulfate, filtered, and solvent was removed in vacuo. Ethanol was added to the residual amorphous solid and then removed in vacuo. The pure RS-RS diester, compound B, (200 mg, 44% recovery, the second major peak elutin from the column) as well as the pure RR-RS diester (50 mg, 12% recovery, the first major peak eluting from the column) were obtained as amorphous solids. Both compounds were essentially one peak when analyzed by HPLC** with retention times 31 and 29 minutes respectively.

RS-RS diester: Anal. Calcd. for $C_{58}H_{80}Cl_2N_2O_{14}\cdot 5H_2O$: C, 58.53; H, 7.62; N, 2.35; Cl, 5.96. Found C, 58.38; H, 7.59; N, 2.30; Cl, 5.98.

Example 2: Biological Activity

The tests employed herein are described by J. J. Savarese (Anesthesia and Analgesia, Vol. 52, No. 6, Nov.-Dec., (1973). Cats were anesthetized with alpha-chloralose (80 mg/kg) and pentobarbital (10 mg/kg) i.p. Monkeys received thiopental (35-40 mg/kg) i.m. followed by halothane (0.5-10% inspired), nitrous oxide (60%) and oxygen (40%) in a nonrebreathing system. In all animals, the trachea was intubated and ventilation was controlled at

**Same conditions of Example 1A

12-15 mL/kg, 18-24 breaths per minute. Animals not receiving inhalation anesthetics were ventilated with room air. The left femoral vein and artery were cannulated for drug administration and for recording of arterial pressure, respectively. Square-wave stimuli were applied at supramaximal voltage to the peroneal nerve at 0.15 Hz and the evoked twitches of the tibialis anterior muscle were recorded. Muscle and animal temperatures were maintained between 35° and 38°C. All recordings were made on a Grass Polygraph recorder. The results of these tests are shown in Table I and Table II below.

European Patent application, 0 080 682/A1 published June 8, 1983 discloses (trans-trans)-2,2'-(hexamethylenebis(carbonyloxytrimethylene))bis-(1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinoli chloride tosylate, hereinafter referred to as compound "C", as an intermediate acting neuromuscular blocking agent.

The data in tables I and II were obtained by sequential administration of escalating dosages of each compound. In practice, such compounds are normally administered by single bolus.

Table 1

Neuromuscular Blocking Activity of the Compound A of Formula (I) and Compound C of O 080 682/A1

COMPOUND	CAT		RHESUS MONKEY		
	ED_{95} (mg/kg)[a]	Duration (min)[b]	ED_{95} (mg/kg)[a]	Duration (min)[b]	Therapeutic Ratio[c]
A (Example 1a)	0.04-0.06	12-16	0.03-0.04	9-13	20
C (O 080 682/A1)	0.06-0.08	38-50	0.06	17	6.7

[a]Intravenous dose producing 95% neuromuscular paralysis of the tibialis anterior twitch extrapolated from dose-response curves. The ED_{95} neuromuscular blocking dose is determined because it is related to the degree of muscular paralysis needed to safely facilitate a rapid and easy intubation when neuromuscular blocking agents are used therapeutically.

[b]The time from intravenous injection to 95% recovery.

[c]Therapeutic ratio is the dose producing adverse cardiovascular effects (A, 0.8 mg/kg and C, 0.4 mg/kg) divided by the ED_{95}. The greater this ratio, the greater the safety level.

SP2B/sp/13

Table II

Direct Comparison of Compound A (Diastereomeric Mixture) and Compound B (RS-RS Diastereomer of A) in Cats and Rhesus Monkey

	CAT			RHESUS MONKEY		
Compound	dose (mg/kg)	%block	duration[b] (min)	dose (mg/kg I.V.)	%block	duration[b] (min)
A	0.04	56±12	10±2	0.02	27	6
(Example 1a)	0.05	78±10	13±1	0.04	99	12
B	0.04	79±4	12±2	0.02	83	11
(Example 1b)	0.05	96±3	14±3	0.03	100	13

[b]The time from intravenous injection to 95% recovery.

Table 1 shows that a compound of ths invention, Compound A, is more potent and significantly shorter acting than Compound C disclosed in the art. Compound C would be unacceptable as a short acting agent on the basis of its duration of action.

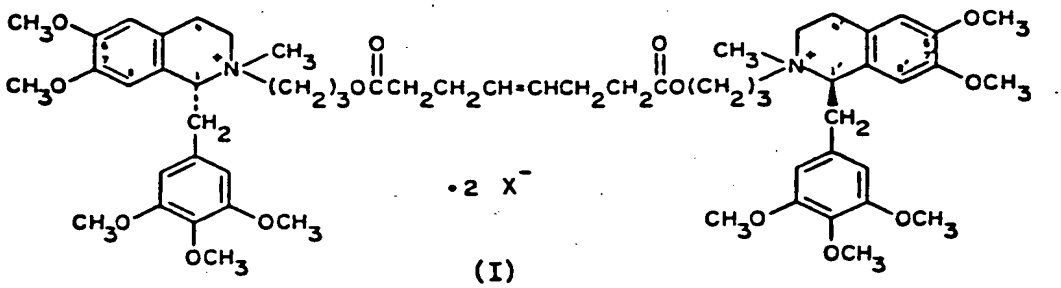
Table II shows that in the cat and rhesus monkey Compound A and Compound B have the same neuromuscular blocking profiles except that in both species Compound B is at least 20-25 percent more potent than Compound A.

Examole 3: Toxicitv

Three groups of four beagle dogs each were treated twice weekly for three weeks with vehicle, Compound A at five times the ED_{100} or Compound A at fifteen times the ED_{100}. Each treatment session consisted of an initial bolus injection followed by a continuous infusion for two hours. All of the dogs were anesthetized with pentobarbital and artificially ventilated during the sessions. All of the dogs survived, and no deleterious effects were observed.

We claim:

1. A compound of the formula (I)



(I)

wherein X is a pharmaceutically acceptable anion.

2. A compound of claim 1 wherein the central double bond is in the (E) configuration (trans).

3. A compound of claim 2 which is the RS-RS (trans-trans) diastereomer or the RR-RS (cis-trans) diastereomer.

4. A mixture comprising the RS-RS (trans-trans), RS-RR (trans-cis) and RR-RR (cis-cis) diastereomers of a compound of the formula (I) as described in claim 2.

5. A pharmaceutical composition for use as a muscle relaxant comprising a compound of formula I described in claim 1, in association with a pharmaceutically acceptable carrier.

6. A method of producing muscle relaxation in a mammal which comprises parenterally administering to a mammal a compound of formula (I) as described in claim 1, 2, 3 or 4.

7. The method of claim 6 in which the compound is administered in a pharmaceutically acceptable carrier.

8. A compound of claim 1 where X is Cl.

9. A mixture according to claim 4 wherein X is Cl.

10. A composition according to claim 5 wherein X is Cl.

11. A method according to claim 6 wherein X is Cl.

12. The method of preparing the compound or salt of claim 1 to 4 according to disclosure and examples.

13. A pharmaceutical formulation prepared by mixing a compound or salt of claims 1 to 4 with a solvent therefore.